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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,186	02/04/2002	John Walter Liebeschuetz	00218/US	8449

24330 7590 10/29/2003  
Martin A. Hay  
13 Queen Victoria Street  
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UNITED KINGDOM

EXAMINER

LIU, HONG

ART UNIT PAPER NUMBER

1624

8

DATE MAILED: 10/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/030,186

Applicant(s)

LIEBESCHUETZ ET AL.

Examiner

Hong Liu

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-13,16-21,24 and 27-31 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-13,16-21,24 and 27-31 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

### DETAILED ACTION

Claims 1-13, 16-21, 24, and 27-31 are pending in this application.

#### *Election/Restrictions*

1. Applicant's election without traverse of species of Example 17 in Paper No. 7 is acknowledged.

The elected compound was not found to be anticipated in the search and the search was expanded to the whole genus.

#### *Claim Rejections - 35 USC § 112*

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-13, 16-21, 24, and 27-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preparation of compounds wherein the core of  $-L-Lp(D)_n$  is a piperidine, R2 is indole, phenyl, and piperidine, does not reasonably provide enablement for preparation and use of compounds wherein the core of  $-L-Lp(D)_n$  is pyrrolidine, and R2 is any aromatic ring. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The nature of the invention in the instant application has claims which embrace a diversity of chemically and physically distinct compounds, wherein R2 can be an unsubstituted or substituted, mono or polyaromatic or an unsubstituted or substituted, mono or poly-

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heteroaromatic group, containing one or more heteroatoms, etc. While many compounds are disclosed, there is insufficient guidance for preparing additional serine protease inhibitors which would be effective since the cited examples are drawn to a homogenous group of compounds not remotely commensurate in scope to applicants' claims. Only compounds wherein the  $-L-Lp(D)_n$  core contains piperidine rather than pyrrolidine, R2 is indole, phenyl, piperidine have been made.

Furthermore, testing data is limited to a number of compounds not considered to be representative of all the possible compounds encompassed by the claims. Examples should be of sufficient scope as to justify the scope of the claim. However, the generic claims are much broader in scope than is represented by the testing. The definitions of the  $-L-Lp(D)_n$  core variables embrace many structurally divergent groups not represented at all in testing, since testing for the instant compounds is not seen in the specification. Markush claims must be provided with support in the disclosure when the "working examples" fail to include written description(s) which teach how to make and use Markush members embraced thereby in full, clear and exact terms. See *In re Fouch*, 169 USPQ 429.

This area of activity can be expected to be highly structure specific and unpredictable, as is generally true for chemically-based pharmacological activity. In view of the structural divergence in the claims, one skilled in the art could not reasonably extrapolate the activities of some of the claimed compounds to the other structurally divergent compounds embraced by the claims which have not been tested. In cases directed to chemical compounds which are being used for their physiological activity, the scope of the claims must have a reasonable correlation to the scope of enablement provided by the specification. See *In re Surrey* 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. No reasonable assurance has been made

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that the instant compounds as an entire class have the required activities needed to practice the invention. Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability” have been demonstrated to be sufficiently lacking in the instant case for the scope being claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1). The use of “5 or 6 membered heterocyclic ring” in the definition of R variables is unclear to the array of heteroatoms, size of the rings, as well as nature of atoms as ring members. See *In re Wiggins* 179 USPQ 421 for certain terminology regarding heterocyclic ring systems.

2). Claim 24 is of indeterminate scope because no one particular thrombotic disorder is recited.

3). In Claim 1, page 3 of the preliminary amendment, line 4, the phrase “a 3, 4-didehydro derivative” recites more than what is positively described.

### ***Claim Rejections - 35 USC § 103***

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-5, 10-13, 21, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liebeschuetz et al. (WO 99/11657). The reference teaches a generic group of compounds which embraces applicant's instantly claimed compounds. See formula I, Col. 2 wherein the functional group corresponding to R<sub>2</sub> of the present application is amino-7-isoquinoline and R is X-X-Y(R<sub>7</sub>)-L-Lp(D)<sub>n</sub>. Example 54 in the reference would have anticipated the claims of the present application if the proviso that R<sub>2</sub> "cannot be aminoisquinolyl" in the present application had not been added. However, the functional group of the reference corresponding to R<sub>2</sub> is not limited to aminoisquinolyl. When the dotted line is absent, the functional group becomes a dihydroisoquinoline which has not been excluded by the proviso. The compounds are taught to be useful as serine protease inhibitors. It would have been obvious to one skilled in the art at the time of the invention to be motivated to select any of the species of the genus taught by the reference including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the specie of the genus would have similar properties and, thus, the same use as taught for the genus as a whole. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render *prima facie* obvious a species falling within a genus. See *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. V. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

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***Claim Objections***

Claim 11 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should be in the alternative form. See MPEP § 608.01(n).

**Information Disclosure Statement**

Receipt is acknowledged of the Information Disclosure Statement(s) filed on July 14, 2003. References B3, B7-B20, and C1 were not available to the examiner and therefore, were not considered. The references will be considered in due course if a copy is provided.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Liu whose telephone number is 703 3065814. The examiner can normally be reached on 8:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 703 308 4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703 308-4556 for regular communications and 703 3084734 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 358-1235.



**Mukund Shah  
Supervisory Patent Examiner  
Art Unit 1624**

hl  
October 23, 2003